

What is claimed is:

1. A process for making quetiapine comprising the step of reacting 11-piperazinyl dibenzo[*b,f*]-[1,4]thiazepine hydrochloride and 2-(2-chloroethoxy) ethanol in a solvent in the presence of a base, and a phase transfer catalyst.

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2. The process of claim 1 wherein the reacting is at reflux temperature.

3. The process of claim 1 wherein the reacting is performed in the presence of an alkali metal halide.

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4. The process of claim 3 wherein said alkali metal halide is sodium iodide.

5. The process of claim 1 wherein the phase transfer catalyst is selected from the group consisting of tetrabutylammonium bromide, triethylbenzylammonium chloride, tricaprylmethylammonium chloride and tetrabutylammonium hydroxide.

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6. The process of claim 5 wherein the phase transfer catalyst is tetrabutylammonium bromide.

7. The process of claim 1 wherein the solvent is a lower alkanol, an aromatic hydrocarbon, or dipolar aprotic solvent, or a mixture of one or more of these.

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8. The process of claim 7 wherein the solvent is *n*-butanol.

9. The process of claim 7 wherein the solvent is toluene.

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10. The process of claim 7 wherein the solvent is dimethyl formamide.

11. The process of claim 1 wherein the base is selected from the group consisting of an alkali metal and alkaline earth metal oxides, hydroxides, bicarbonates and carbonates.

12. The process of claim 11, wherein said base is sodium carbonate.

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13. A process for making quetiapine hemifumarate comprising the steps of:

a) reacting 11-piperazinyl dibenzo[*b,f*]-[1,4]thiazine hydrochloride and 2-(2-chloroethoxy)ethanol in a solvent in the presence of a base, and a phase transfer catalyst, whereby a first slurry is obtained,

10 b) separating the solid from the first slurry whereby a liquid filtrate is obtained,

c) combining the liquid filtrate with fumaric acid, whereby a second slurry is obtained, and

d) isolating quetiapine hemifumarate from the second slurry.

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14. The process of claim 13 wherein the combination of step c) is heated to a temperature of about 80°C to about 100° C or higher and subsequently cooled to a temperature less than about 100° C, whereby a slurry is obtained.

20 15. The process of claim 13 wherein the reacting is at a temperature of about 100°C.

16. The process of claim 13 wherein the reacting is performed in the presence of an alkali metal halide.

25 17. The process of claim 16 wherein said alkali metal halide is sodium iodide.

18. The process of claim 13 wherein the phase transfer catalyst is selected from the group consisting of tetrabutylammonium bromide, triethylbenzylammonium chloride, tricaprylmethylammonium chloride, and tetrabutylammonium hydroxide.

19. The process of claim 18 wherein the phase transfer catalyst is tetrabutylammonium bromide.
- 5 20. The process of claim 13 wherein the solvent is a lower alkanol, an aromatic hydrocarbon, or dipolar aprotic solvent, or a mixture of one or more of these.
21. The process of claim 20 wherein the solvent is *n*-butanol.
- 10 22. The process of claim 20 wherein the solvent is toluene.
23. The process of claim 20 wherein the solvent is dimethyl formamide.
24. The process of claim 13 wherein the base is selected from the group consisting of
15 an alkali metal and alkaline earth metal oxides, hydroxides, bicarbonates and carbonates.
25. The process of claim 24 wherein the base is sodium carbonate.
26. The process of claim 13 further comprising the step of recrystallizing the
20 isolated quetiapine hemifumarate from a solvent selected from the lower alkanols and mixtures of a dipolar aprotic solvent and water.
27. The process of claim 26 wherein the lower alkanol is ethanol or isopropanol and the dipolar aprotic solvent is dimethyl formamide.
- 25 28. In a process for making quetiapine or a pharmaceutically acceptable salt thereof, the step of reacting 11-piperazinyl dibenzo[*b,f*]-[1,4]thiazepine hydrochloride and 2-(2-chloroethoxy)ethanol in a solvent that is a lower alkanol, an aromatic hydrocarbon, or a

dipolar aprotic solvent, in the presence of sodium carbonate, sodium iodide, and tetrabutylammonium bromide.

29. The process of claim 28 wherein the pharmaceutically acceptable salt is the
5 hemifumarate.

30. A process for making quetiapine comprising the step of reacting, at reflux, 11-piperazinyl dibenzo[*b,f*]-[1,4]thiazepine hydrochloride and 2-(2-chloroethoxy)ethanol in a solvent selected from n-butanol, toluene, and dimethyl formamide, in the presence of
10 sodium carbonate, sodium iodide, and tetrabutylammonium bromide.

31. A process for making quetiapine hemifumarate comprising the steps of:
a) reacting, at reflux, 11-piperazinyl dibenzo[*b,f*]-[1,4]thiazepine hydrochloride and 2-(2-chloroethoxy)ethanol in a solvent selected from n-butanol, toluene, and dimethyl
15 formamide in the presence of sodium carbonate, and tetrabutyl ammonium bromide, whereby a first slurry is obtained,

b) separating the solid from the first slurry whereby a liquid filtrate is obtained,

c) combining the liquid filtrate with fumaric acid,

20 d) heating the combination to a temperature of about 100°C or higher,

e) subsequently cooling the combination to < 100° C, whereby a second slurry is obtained, and

f) isolating quetiapine hemifumarate from the second slurry.

25 31. The process of claim 30 wherein the rereacting is carried-out also in the presence of sodium iodide.

32. The process of claim 30 further comprising the step of recrystallizing the quetiapine hemifumarate isolated in step f) from a solvent selected from the lower alkanol
30 or a mixture of a dipolar aprotic solvent and water.

33. The process of claim 32 wherein the lower alkanol is ethanol or isopropanol and the dipolar aprotic solvent is dimethyl formamide.